A REVIEW ON THE DIVERSE EFFECTS OF D-PINITOL

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ABSTRACT
D-Pinitol, a mono-methylated form of D-chiro-inositol, was identified as an active principle in soy foods and legumes. Mature and dried soybean seeds contain up to 1% D-pinitol. D-pinitol functions in plants as an osmolyte by improving the tolerance to drought stress or heat stress. Pinitol has well-known insulin-like effects. In addition, D-pinitol possess multifunctional properties, including feeding stimulant, anti-inflammatory, cardioprotective, anti-hyperlipidemic and creatine retention promotion properties. Recent studies have shown potential chemotherapeutic efficacy against cancers of the lung, bladder and breast. In addition, D-pinitol has been reported to reduce metastasis of human lung cancers. This review is an attempt to summarize the different effects of D-Pinitol in a brief manner.

Keywords: D-Pinitol; Pancreas; oxidative stress; Liver; Hyperlipidemia; Prostate cancer

INTRODUCTION
D-Pinitol is a cyclitol, a cyclic polyol. It is a known anti-diabetic agent isolated from Sutherlandia frutescens leaves [1]. Gall plant tannins can be differentiated by their content of pinitol. It was first identified in the sugar pine (Pinus lambertiana) [2]. It is also found in other plants, such as in the pods of carob tree [3].
Pinitol (3-O-methyl-chiro-inositol) is a monomethylated form of D-chiro-inositol, which is one chiral form of cyclohexitol [4]. It is a naturally occurring compound found in pine wood, alfalfa, and legumes, but is generally derived from soy or carob for manufacturing purpose [5, 6]. Pinitol has well-known insulin-like effects, driving creatine in addition to other nutrients into the muscle cells. [7]
rats is also reported. It is suggested that pinitol could prevent cardiovascular diseases, and could inhibit ovalbumin-induced airway inflammation in rats [8-11].

EFFECTS OF D-PINITOL

2.1 Role of D-Pinitol in protecting the pancreas from oxidative stress

Sivakumar & Subramanian [12] evaluated the pancreatic protective nature of D-Pinitol in experimental rats. It was examined by determining the activity of pancreatic enzymatic antioxidants such as superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) and glutathione-S-transferase (GST). To assess the extent of oxidative stress, the levels of lipid peroxidation (LPO) and hydroperoxides in both plasma and pancreatic tissues were also measured in experimental rats. A significant increase in the levels of both lipid peroxides and hydroperoxides with a concomitant decrease in antioxidant status was observed in the diabetic rats when compared to control rats. Oral administration of D-Pinitol (50 mg/kg b.w./day for 30 days), ameliorates the free radical-mediated alterations to near normalcy. The results of the study suggested that D-Pinitol protects the pancreatic tissue from free radical-mediated oxidative stress in addition to its antidiabetic property [13].

2.2 Role of D-Pinitol in preventing lipid peroxidation by increasing cellular antioxidant levels

Oxidative stress has been reported as one of the major causes of tissue damage. Excessive production of free radicals resulting from oxidative stress can damage macromolecules. Increase in malondialdehyde (MDA) is an indicator of oxidative stress [14]. Glutathione is an important endogenous antioxidant that is found in a particularly high concentration in the liver and has key functions in protective processes. The reduced form of GSH becomes readily oxidized to GSSG when interacting with free radicals and can induce lipid peroxidation in vivo. GR, which is an important antioxidative enzyme, reduces GSSG to GSH. Supplementation with pinitol significantly decreased MDA, and elevated the levels of GSH and antioxidative enzyme activities. The study suggests that pinitol might have an antioxidative effect or stimulative effect on the antioxidative enzyme system, which might contribute to its ability to maintain the cellular GSH level and to suppress lipid peroxidation [14].

2.3 Role of D-pinitol against D-galactosamine (GalN) induced liver damage in rats

GalN-induced hepatotoxicity is well established as morphologically and functionally similar to human viral hepatitis. The liver damage induced by GalN generally reflects a disturbance of liver cell metabolism, which leads to characteristic changes in serum enzyme activity. The increased levels of ALT and AST may be interpreted as a result of liver cell destruction or a change in membrane permeability [15]. These enzymes are characteristic of liver damage; therefore, their release into the serum confirms GalN-induced liver damage. It is reported that pinitol supplementation at the level of 0.5%

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markedly decreased the elevated enzyme activity induced by GalN. Pinitol supplementation was reported to have a hepatoprotective effect against the liver damage induced by GalN in rats [15, 16].

2.4 Role of D-Pinitol in preventing hyperlipidemia in experimental Diabetes mellitus

Studies from STZ-induced diabetic rats showed significant increase in the levels of blood glucose and total cholesterol, triglycerides, free fatty acids, and phospholipids in serum, liver, kidney, heart, and brain. The levels of low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) cholesterol were significantly increased, and the level of high-density lipoprotein (HDL) cholesterol was significantly decreased in diabetic rats. Oral administration of D-pinitol to STZ-induced diabetic rats showed significant decrease in the levels of blood glucose and total cholesterol, triglycerides, free fatty acids, and phospholipids in serum, liver, kidney, heart, and brain. The D-pinitol also lowered significantly LDL and VLDL cholesterol levels and increased significantly HDL cholesterol levels in the serum of diabetic rats. This study clearly reported the antihyperlipidemic effect of D-pinitol in STZ-induced type II Diabetes mellitus [17].

2.5 Role of D-Pinitol in modulating genotoxin mediated toxic effects

7,12 dimethyl benz(a)anthracene (DMBA) is a well-known environmental carcinogen and a genotoxin [18]. It is known to cause breast carcinogenesis in different studies. Studies show that administration of D-Pinitol significantly down regulated the breast tissue glycoproteins and lysosomal enzymes and in contrast the levels of adenosine triphosphatases were remarkably up regulated. D-Pinitol efficiently attenuated the hazardous consequences of the environmental carcinogen DMBA through modulating cell surface glycoproteins, membrane protective role both in lysosomal and ATPase compartment via its antioxidant nature which ultimately results in the findings of future innovative remedies for genotoxin mediated hazards [18, 19].

2.6 Role of D-pinitol against Prostate Cancer Metastasis

Integrins, which link the extracellular matrix to intracellular signaling molecules, regulate a number of cellular processes, including adhesion, signaling, motility, survival, gene expression, growth and differentiation. It has been reported that disintegrin or a αvβ3 integrin antibody blocked cancer migration and metastasis. Studies reported that D-pinitol reduced the mRNA expression of αv and β3 integrin. Furthermore, treatment of prostate cancer cells with D-pinitol also diminished the cell surface expression of αvβ3 integrin. This indicates that αvβ3 integrin plays an important role in the D-pinitol-inhibited metastasis of prostate cancer cells. It is found that D-pinitol reduced the migration and the invasion of prostate cancer cells (PC3 and DU145) at noncytotoxic concentrations [20]. Integrins are the major adhesive molecules in mammalian cells and have been associated with the metastasis of cancer cells. Treatment of prostate cancer
cells with D-pinitol reduced mRNA and cell surface expression of αvβ3 integrin. In addition, D-pinitol exerted its inhibitory effects by reducing focal adhesion kinase (FAK) phosphorylation, c-Src kinase activity and NF-κB activation. D-pinitol may be a novel anti-metastasis agent for the treatment of prostate cancer metastasis [20].

2.7 Role of D-pinitol in stimulating the translocation of glucose transporter 4 in skeletal muscle

Diabetes mellitus is a complex disease that is characterized by the defect of insulin sensitivity in such peripheral tissues like skeletal muscle, adipose tissue and liver. It is reported that oral intake of D-pinitol affects GLUT4 translocation in the skeletal muscle of mice [21]. D-Pinitol administration resulted in increasing GLUT4 translocation in the skeletal muscle and lowering the plasma glucose and insulin levels. Thus it is reported that D-Pinitol have the potential to prevent diabetes mellitus by reducing the postprandial blood glucose level and stimulating GLUT4 translocation in the skeletal muscle [21].

2.8 Role of D-Pinitol against Alzheimer's-associated Aβ oligomers

Alzheimer's disease (AD) is a progressive dementia that correlates highly with synapse loss. This loss appears due to the synaptic accumulation of toxic Aβ oligomers (ADDLs), which damages synapse structure and function. Although it has been reported that oligomer binding and toxicity can be prevented by stimulation of neuronal insulin signaling with PPARγ agonists, these agonists have problematic side effects. Pitt et al [22] investigated the therapeutic potential of chiro-inositol, insulin-sensitizing compounds safe for human consumption. Chiro-inositol have been studied extensively for treatment of diseases associated with peripheral insulin resistance, but their insulin mimetic function in memory-relevant central nervous system (CNS) cells is unknown. Hence they demonstrated that mature cultures of hippocampal neurons respond to d-chiro-inositol (DCI), pinitol (3-O-methyl DCI), and the inositol glycan INS-2 (pinitol β-1-4 galactosamine) with increased phosphorylation in key upstream components in the insulin-signaling pathway (insulin receptor, insulin receptor substrate-1, and Akt). Consistent with insulin stimulation, DCI treatment promotes rapid withdrawal of dendritic insulin receptors. With respect to neuroprotection, DCI greatly enhances the ability of insulin to prevent ADDL-induced synapse damage (EC(50) of 90 nM). The mechanism comprises inhibition of oligomer binding at synapses and requires insulin/IGF signaling. DCI showed no effects on Aβ oligomerization. Thus it is studied that inositol glycans and DCI, a compound already established as safe for human consumption, have potential as AD therapeutics by protecting CNS synapses against Aβ oligomers through their insulin mimetic activity [22].

2.9 Role of D-pinitol in regulating Th1/Th2 balance via suppressing Th2 immune response in ovalbumin-induced asthma.

D-pinitol has been demonstrated to exert insulin-like and anti-inflammatory
activities. However, its anti-allergic effect in the Th1/Th2 immune response is poorly understood. Recently, it was shown that T-bet and GATA-3 are master Th1 and Th2 regulatory transcription factors. In the study from Lee et al. [23], they have attempted to determine whether D-pinitol regulates Th1/Th2 cytokine production, T-bet and GATA-3 gene expression in OVA-induced asthma model mice. They also examined to ascertain whether D-pinitol could influence eosinophil peroxidase (EPO) activity. After being sensitized and challenged with ovalbumin (OVA) showed typical asthmatic reactions. These reactions included an increase in the number of eosinophils in bronchoalveolar lavage (BAL) fluid, an increase in inflammatory cell infiltration into the lung tissue around blood vessels and airways, airway luminal narrowing, and the development of airway hyper-responsiveness (AHR). The administration of D-pinitol before the last airway OVA challenge resulted in a significant inhibition of all asthmatic reactions. Accordingly, this study may provide evidence that D-pinitol plays a critical role in the amelioration of the pathogenetic process of asthma in mice. These findings provide new insight into the immunopharmacological role of D-pinitol in terms of its effects in a murine model of asthma, and also broaden current perspectives in the understanding of the immunopharmacological functions of D-pinitol [23].

CONCLUSION

To conclude, this review focusses briefly on the plausible divergent actions of D-Pinitol and its benefits. This will pave way for knowing more about the mechanism and further actions of D-Pinitol and its therapeutic effects in a detailed manner in future.

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